Technical Project Lead (TPL) Review:

SE0002998, SE0003000, SE0003001, SE0003005, SE0003006, SE0003012, SE0003014, SE0003015, and SE0003020 - SE0003023

SE0002998: Smokin Joes Menthol Gold King Size Soft Pack Fire Safe	
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.8 mm
Ventilation	6 %
Characterizing Flavor	Menthol
SE0003000: Smokin Joes Menthol King Size Soft Pack Fire Safe	
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.8 mm
Ventilation	2 %
Characterizing Flavor	Menthol
SE0003001: Smokin Joes Menthol King Size Box Fire Safe	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.8 mm
Ventilation	2 %
Characterizing Flavor	Menthol
SE0003005: Smokin Joes Red 100 Size Box Fire Safe	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.8 mm
Ventilation	2 %
Characterizing Flavor	None
SE0003006: Smokin Joes Red 100 Size Soft Pack Fire Safe	
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.8 mm
Ventilation	2 %
Characterizing Flavor	None

SE0003012: Smokin Joes Natural Menthol 100 Size Soft Pack Fire Safe	
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.8 mm
Ventilation	4 %
Characterizing Flavor	Menthol
SE0003014: Smokin Joes Natural Menthol King Size Box Fire Safe	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.8 mm
Ventilation	2 %
Characterizing Flavor	Menthol
SE0003015: Smokin Joes Natural Menthol Gold 100 Size Soft Pack Fire Safe	
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.8 mm
Ventilation	4 %
Characterizing Flavor	Menthol
SE0003020: Smokin Joes Natural Purple 100 Size Box Fire Safe	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.8 mm
Ventilation	2 %
Characterizing Flavor	None

SE0003021: Smokin Joes Natural Purple 100 Size Soft Pack Fire Safe	
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.8 mm
Ventilation	2 %
Characterizing Flavor	None
SE0003022: Smokin Joes Natural Purple King Size Box Fire Safe	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.8 mm
Ventilation	13 %
Characterizing Flavor	None
SE0003023: Smokin Joes Natural Purple King Size Soft Pack Fire Safe	
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.8 mm
Ventilation	13 %
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	Joseph Anderson d/b/a Smokin Joes
Report Type	Provisional
Product Category	Cigarette
Product Sub-Category	Combusted Filtered
Recommendation	
Issue Not Substantially Equivalent (NSE) orders.	

Technical Project Lead (TPL):

Matthew J. Walters -S
2018.08.21 09:18:31 -04'00'

Matthew J. Walters, Ph.D., M.P.H.
CDR, U.S. Public Health Service
Deputy Director
Division of Product Science

Signatory Decision:

☒ Concur with TPL recommendation and basis of recommendation

☐ Concur with TPL recommendation with additional comments (see separate memo)

☐ Do not concur with TPL recommendation (see separate memo)

Digitally signed by Matthew R. Holman -S
Date: 2018.08.21 16:42:24 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

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1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCTS

The applicant submitted the following predicate tobacco products:

SE0002998: Smokin Joes Menthol Gold King Size Soft Pack Fire Safe	
Product Name	Smokin Joes Menthol Light King Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	Menthol
SE0003000: Smokin Joes Menthol King Size Soft Pack Fire Safe	
Product Name	Smokin Joes Menthol King Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	Menthol
SE0003001: Smokin Joes Menthol King Size Box Fire Safe	
Product Name	Smokin Joes Menthol King Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	Menthol
SE0003005: Smokin Joes Red 100 Size Box Fire Safe	
Product Name	Smokin Joes Full Flavor 100's Box
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	None

SE0003006: Smokin Joes Red 100 Size Soft Pack Fire Safe	
Product Name	Smokin Joes Full Flavor 100's Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	None
SE0003012: Smokin Joes Natural Menthol 100 Size Soft Pack Fire Safe	
Product Name	Smokin Joes Natural Menthol 100's Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	Menthol
SE0003014: Smokin Joes Natural Menthol King Size Box Fire Safe	
Product Name	Smokin Joes Natural Menthol King Box
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	Menthol
SE0003015: Smokin Joes Natural Menthol Gold 100 Size Soft Pack Fire Safe	
Product Name	Smokin Joes Natural Menthol Light 100's Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	Menthol

SE0003020: Smokin Joes Natural Purple 100 Size Box Fire Safe	
Product Name	Smokin Joes Natural Full Flavor 100's Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	None
SE0003021: Smokin Joes Natural Purple 100 Size Soft Pack Fire Safe	
Product Name	Smokin Joes Natural Full Flavor 100's Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	None
SE0003022: Smokin Joes Natural Purple King Size Box Fire Safe	
Product Name	Smokin Joes Natural Full Flavor King Box
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	None
SE0003023: Smokin Joes Natural Purple King Size Soft Pack Fire Safe	
Product Name	Smokin Joes Natural Full Flavor King Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter	7.91 mm
Ventilation	0 %
Characterizing Flavor	None

The predicate tobacco products are combusted filtered cigarettes manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 22, 2011, FDA received 12 SE Reports (SE0002998, SE0003000, SE0003001, SE0003005, SE0003006, SE0003012, SE0003014, SE0003015, and SE0003020 - SE0003023) from Joseph Anderson d/b/a Smokin Joes (Smokin Joes). FDA issued Acknowledgement letters on August 31, 2011. On June 4, 2012, FDA corresponded via fax requesting the applicant to identify any inaccuracies or omissions for each proposed tobacco product name and corresponding STN.[1] On June 8, 2012, FDA received the applicant's amendment (SE0004569) in response to the June 4, 2012, fax. On November 8, 2012, and November 20, 2012, FDA conducted teleconferences, as part of the FDA data clean-up process, to clarify tobacco product names and identify discontinued tobacco products.

On October 31, 2012, Public Health Impact (PHI) reviews were completed, and these SE Reports were assigned to PHI Tier 1. Upon further review of the amendments submitted by the applicant, including information on product composition, FDA reassigned all of the products to PHI Tier 2 on May 9, 2013.

On December 14, 2012, FDA received an unsolicited amendment (SE0009929) for STNs SE0002998, SE0003000, SE0003001, SE0003012, SE0003014 and SE0003015 regarding a change in the manufacturing of their mentholated tobacco products.[2] On December 28, 2012, FDA issued Advice/Information (A/I) Request letters for these SE Reports. On January 18, 2013, FDA received a 30-day extension request (SE0006310) to respond to the December 28, 2012, A/I Request letters. On January 31, 2013, FDA conducted a teleconference to inform the applicant that the responses to the December 28, 2012, A/I Request letters would not be due on January 27, 2013, and that FDA would be issuing a letter with further instructions.[3] On February 28, 2013, FDA received amendments (SE0007507, SE0007615, SE0007616, SE0007618, SE0007575, SE0007576, SE0007577, SE0007578, SE0007581-SE0007584) in response to the December 28, 2012, A/I Request letters.

On March 4, 2013, FDA emailed Smokin Joes to request further clarification of tobacco product names and to specify package type and package quantity for all SE Reports. On March 19, 2013, FDA received an amendment (SE0009117) in response to the March 4, 2013, email.

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[1] The applicant included the June 4, 2012, FDA fax correspondence in its amendment SE0004569.

[2] Smokin Joes identified that SE0002998, SE0003000, SE0003001, SE0003012, SE0003014 and SE0003015 had a change in the manner of menthol application (b) (4) [redacted] A new tobacco product includes "any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007." Section 910(a)(1)(B) of the Federal Food, Drug and Cosmetic Act. (b) (4) [redacted], such new tobacco products would not have been first introduced or delivered into interstate commerce for commercial distribution after February 15, 2007, and prior to March 22, 2011 and thus, unless grandfathered, could not be legally marketed without first undergoing premarket review. Section 910(a)(2) of the FD&C Act. See section 4.1 of this memorandum discussing the application of menthol to the new products.

[3] A notification letter issued later with instructions regarding amendments and the start of the substantive scientific review process.

On July 9, 2013, FDA issued a Correction letter informing Smokin Joes that FDA had revised the records to include clarifications to the new tobacco product names. On July 31, 2013, FDA received an amendment (SE0009439) in response to the July 9, 2013, Correction letter, which also addressed a voicemail and several e-mails from the Office of Compliance and Enforcement regarding clarification of the grandfathered predicate tobacco product names.

FDA issued a Notification letter on November 10, 2014, informing Smokin Joes that scientific review of these SE Reports would begin on December 26, 2014. On December 23, 2014, FDA received an amendment (SE0010816) in response to the November 10, 2014, Notification Letter, which included amended design features, ingredients, and materials data, grandfathered predicate tobacco product information, and new tobacco product information. On January 27, 2016, FDA received a 90-day extension request (SE0012816) for FDA to delay taking action on Smokin Joes' SE Reports. On February 9, 2016, FDA received an amendment (SE0012859) to clarify the January 27, 2016, extension request and provide a new tobacco product name for SE0003015. FDA issued a General Correspondence letter on March 11, 2016, stating that there is no basis for an extension request, since there is no timeframe for response currently requested in an A/I Request letter or a Preliminary Finding (Pfind) letter. FDA had conversations with the applicant regarding all products currently submitted under an application (e.g., SE Report) and on November 23, 2016, a General Correspondence letter was issued where FDA agreed to delay review until March 10, 2017 as long as certain conditions were met by Smokin Joes. This delay in review enabled Smokin Joes to provide information, similar to the information requested in the August 19, 2016 PFind letter and the September 7, 2016 A/I Request letter issued to SE Reports in other Smokin Joes batches[4], for these SE Reports.

On March 10, 2017, FDA received a partial response (SE0013970) to the November 23, 2016, General Correspondence letter, and certificates of analysis (SE0013969). On March 24, 2017, FDA received an unsolicited amendment (SE0013992) requesting a 120-day extension of time to provide a complete response to the November 23, 2016, General Correspondence letter; the applicant stated that the extension request was due to incomplete new tobacco product testing by a third-party testing laboratory. On June 16, 2017, FDA issued a General Correspondence letter, granting the applicant until July 10, 2017, to respond to the November 23, 2016, General Correspondence letter.

On July 10, 2017, FDA received an amendment (SE0014198) in response to the June 16, 2017, General Correspondence letter. FDA held a telecon with Smokin Joes on August 23, 2017, requesting clarification on predicate product information provided for SE0003023. On August 30, 2017, FDA received a response (SE0014293) to the predicate product information requested for SE0003023. On September 15, 2017, FDA issued an A/I Request letter with a response due date of November 14, 2017. On October 19, 2017, FDA received an amendment (SE0014381) requesting an extension to respond to the September 15, 2017, A/I Request letter. On November 8, 2017, FDA denied this extension request. No response was received from the applicant by the A/I Request letter response due date of November 14, 2017. A PFind letter, conveying all deficiencies and requests previously included in the September 15, 2017 A/I Request letter, was issued on February 13, 2018, with a response due date of March 15, 2018. To date, no response to the February 13, 2018 PFind letter has been received.

[4] The August 19, 2016 PFind letter was issued to SE0004614-SE0004642 and SE0004978 – SE0004990. The September 7, 2016 A/I Request letter was issued to SE0005322, SE0005357-SE0005358, SE0005369-SE0005370, and SE0005422-SE0005424.

On February 15, 2018, FDA held a follow-up telecon in which the Smokin Joes stated they would not be able to respond to any deficiency letters prior to a meeting with FDA on March 7, 2018. Smokin Joes noted they intended to gain advice for all deficiency letters during this March 7, 2018 meeting. Although the meeting was held, to date FDA has not received any response to deficiency letters for these STNs.

Product Name	SE Report	Amendments
Smokin Joes Menthol Gold King Size Soft Pack Fire Safe	SE0002998	SE0004569 SE0009929 SE0006310 SE0007507 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381
Smokin Joes Menthol King Size Soft Pack Fire Safe	SE0003000	SE0004569 SE0009929 SE0006310 SE0007615 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381

Product Name	SE Report	Amendments
Smokin Joes Menthol King Size Box Fire Safe	SE0003001	SE0004569 SE0009929 SE0006310 SE0007616 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381
Smokin Joes Red 100 Size Box Fire Safe	SE0003005	SE0004569 SE0006310 SE0007618 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381
Smokin Joes Red 100 Size Soft Pack Fire Safe	SE0003006	SE0004569 SE0006310 SE0007575 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381

Product Name	SE Report	Amendments
Smokin Joes Natural Menthol 100 Size Soft Pack Fire Safe	SE0003012	SE0004569 SE0009929 SE0006310 SE0007576 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381
Smokin Joes Natural Menthol King Size Box Fire Safe	SE0003014	SE0004569 SE0009929 SE0006310 SE0007577 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381
Smokin Joes Natural Menthol Gold 100 Size Soft Pack Fire Safe	SE0003015	SE0004569 SE0009929 SE0006310 SE0007578 SE0009117 SE0009439 SE0010816 SE0012816 SE0012859 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381

Product Name	SE Report	Amendments
Smokin Joes Natural Purple 100 Size Box Fire Safe	SE0003020	SE0004569 SE0006310 SE0007581 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381
Smokin Joes Natural Purple 100 Size Soft Pack Fire Safe	SE0003021	SE0004569 SE0006310 SE0007582 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381
Smokin Joes Natural Purple King Size Box Fire Safe	SE0003022	SE0004569 SE0006310 SE0007583 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014381

Product Name	SE Report	Amendments
Smokin Joes Natural Purple King Size Soft Pack Fire Safe	SE0003023	SE0004569 SE0006310 SE0007584 SE0009117 SE0009439 SE0010816 SE0012816 SE0013969 SE0013970 SE0013992 SE0014198 SE0014293 SE0014381

1.3. SCOPE OF REVIEW

This review captures all the regulatory, compliance, and scientific reviews completed for these SE Reports.

2. REGULATORY REVIEW

Regulatory reviews were completed by Dan Gonski on:

- December 28, 2012 and April 22, 2013 for SE0002998, SE0003000, SE0003001, SE0003005, SE0003012, SE0003014, SE0003015, SE0003020-SE0003023.
- December 28, 2012 and April 5, 2013 for SE0003006.

These initial reviews concluded that the SE Reports were administratively incomplete because the heating source of the new and predicate products was not included in the SE Reports.

However, this information was provided during the scientific review process. Therefore, the final reviews conclude that the SE Reports are administratively complete.

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed reviews to determine whether the applicant established that the predicate tobacco products are grandfathered products (i.e., were commercially marketed in the United States other than exclusively in test markets as of February 15, 2007). The OCE reviews dated December 9, 2014, conclude that the evidence submitted by the applicant is adequate to demonstrate that the predicate tobacco products are grandfathered and, therefore, are eligible predicate tobacco products.

4. SCIENTIFIC REVIEW

Scientific reviews were completed by the Office of Science (OS) for the following disciplines:

4.1. CHEMISTRY

A chemistry review was completed by Katherine Lovejoy on March 10, 2015. A memo to file was completed by Jikun Liu on August 31, 2017, updating the chemistry review in order to review amendments received in response to the General Correspondence letter after the review was finalized.

The final chemistry review concludes that the new tobacco products have different characteristics related to product chemistry compared to the corresponding predicate tobacco products and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiencies that have *not* been adequately resolved:

1. All of your SE Reports provide information about tobacco and ingredients added to tobacco in the new and predicate products, but limited information on the grades was provided. For example, SE Reports SE0003000 and SE0003001 list the grade of (b) (4) as "to be supplemented." All of your SE Reports list the grade/purity of multiple flavor ingredients as "Natural substance" or "Natural product, no purity or grade assigned." The predicate products in SE0002998, SE0003000, SE0003001, SE0003012, SE0003014 and SE0003015 contain menthol flavor (b) (4) purchased from (b) (4) and the predicate products in SE0002998, SE0003000 and SE0003001 contain (b) (4) top flavor. The purity and form were not reported for the two types of menthols. Without this information, we cannot determine whether the new and predicate products are substantially equivalent. Additionally, the information provided for tobacco does not include sufficient detail to fully identify the composition of the new and predicate products. For example, we are unable to understand the meaning of the tobacco grades: (b) (4) . Furthermore, (b) (4) in all the new products. It is not clear why one grade is listed twice within the same type of tobacco. We need additional information that uniquely identifies the tobacco used in the new and predicate products to ensure that the tobacco and other ingredients used in the new and predicate products are equivalent for both products.[5] If you use a tobacco grading system, it would be helpful to know the tobacco grade (along with an explanation of the grading system) for each type of tobacco used in the new and predicate products. Provide a detailed list including:

    a. Uniquely identifying information for all ingredients (e.g., CAS #, grade/purity, function)
    b. Uniquely identifying information for all tobacco (e.g., tobacco grading system)

[5] The deficiency requires some clarification, as this information is not needed to show that the ingredients are "equivalent" but rather to assess whether there are any differences between the new and predicate product and, if so, to determine whether those differences do not cause the new product to raise different questions of public health.

If a difference exists between the new and corresponding predicate products, provide a rationale for each difference with evidence and a scientific discussion for why the difference does not cause the new product to raise different questions of public health.

2. SE0003006, SE00030012, SE0003014, SE0003015, SE0003020 – SE0003023 provide data comparing the quantities of harmful and potentially harmful constituents (HPHCs) in the new and remanufactured predicate products by submitting amendments dated March 10, 2017, and July 10, 2017. However, your SE Reports lack HPHC yields to fully evaluate changes in (b) (4) and (b) (4) in the new products compared to the corresponding remanufactured predicate products. These ingredient differences between the new and corresponding remanufactured predicate products may cause the new products to raise different questions of public health. Provide scientific evidence and rationale to address why these differences do not cause the new products to raise different questions of public health. One way to provide such data is to measure mainstream smoke yields of the following HPHCs in the new and remanufactured predicate products for SE0003006, SE00030012, SE0003014, SE0003015, SE0003020 – SE0003023:

    a. Formaldehyde
    b. Acrolein

    These HPHC measurements would help determine whether the significant blend changes[6] cause the new products to raise different questions of public health. For example, mainstream smoke yields of formaldehyde and acrolein are needed because (b) (4) may be thermally decomposed to formaldehyde and acrolein, while glycerol can be pyrolyzed to acrolein. Higher levels of (b) (4) and (b) (4) in tobacco products may result in higher quantities of formaldehyde and acrolein in mainstream smoke. The measurement of the HPHC quantities under both International Organization for Standardization (ISO) and Canadian Intense (CI) smoking regimens would best characterize the delivery of the constituents from these products. FDA suggests that appropriate measures be taken to minimize data variability and systematic bias. The suggested measures include, but not limited to, using the same laboratory, the same type of smoking machine, the same methods, similar sample storage conditions and duration, and testing within similar timeframe. In addition, your methods (b) (4) are based on some (b) (4) methods. However, your SE Reports lack method details necessary to fully evaluate the validity of HPHC data.[7] Provide the following information about HPHC testing so that we can fully evaluate the differences in HPHC quantities between the new and remanufactured predicate products:

    c. Reference product datasets (e.g., 1R6F
    d. Quantitative test protocols and method used
    e. Testing laboratory and their accreditation(s)
    f. Length of time between date(s) of manufacture and date(s) of testing

[6] This deficiency contained in the third chemistry review erroneously refers to "significant blend changes" when the correct reference should be to the changes in (b) (4) and (b) (4) levels in the new products. The letter-ready deficiencies in Section 6 correct this reference to "significant blend changes."

[7] This sentence is included in error, and has been removed from the letter-ready deficiencies.

g. Number of replicates
h. Standard deviation(s)
i. Complete data sets
j. A summary of the results for all testing performed
k. Storage conditions prior to initiating testing If your test methods are national or international test standards, identify any deviations from those standards.

3. SE0002998, SE0003000, SE0003001, SE0003012, SE0003014, and SE0003015 state the manufacturing process has changed and that the menthol is added to the tobacco instead of the filter as of October 15, 2012. However, your SE Reports SE0002998, SE0003000, SE0003001, SE0003012, SE0003014, and SE0003015 list menthol added to the filter rods as (b) (4) /cigarette in the new products and (b) (4) /cigarette in the predicate products. Clarify the manufacturing process for adding menthol for each new and predicate product and submit new detailed ingredient information for the filter and tobacco for each new and predicate product affected by this manufacturing change. In addition, changes in menthol quantities applied to different locations of a cigarette could result in changes in menthol yields in mainstream smoke that could cause the new products to raise different questions of public health. Provide the absolute quantities of menthol as mg/cigarette in the new and predicate products as well as identify the component that menthol is added. If there is a difference in quantities or application of menthol between the new and corresponding predicate products, provide scientific evidence and rationale why this difference in menthol content does not cause the new products to raise different questions of public health. One way to address this concern is to measure menthol yields in mainstream smoke of the new and predicate products under both the ISO and CI smoking regimens. If the menthol yields are different, explain why the difference does not cause the new products to raise different questions of public health.[8]

4. All of your SE Reports list ingredient quantities as percentages but do not specify the original units of the numerator and denominator, or define the denominator. For some ingredients listed, you do not provide any quantity. In order for us to fully understand the composition of the new and predicate products and make a determination of substantial equivalence, provide ingredient quantities as mass per unit of use (e.g., mg/cigarette).

[8] I as TPL disagree with the chemistry reviewer with respect to the menthol content for these SE Reports. The chemistry review states that a change to the (b) (4)), if any, may result in different menthol yields in the smoke. Menthol is a volatile compound that is known to redistribute between tobacco filler and filter material until an equilibrium concentration is obtained. The redistribution occurs within the first several weeks and results in a consistent menthol content for all cigarettes within a package. However, changes in the total concentration of menthol in a package may result in changes in the amount of menthol in the smoke. The applicant did not provide data or scientific rationale to demonstrate a change in menthol content does not cause the new tobacco products containing menthol to raise different questions of public health. Changes relating to menthol were not evaluated by the Behavioral and Clinical Pharmacology (BCP) reviewer. The available literature focuses on the comparison between non-mentholated relative to mentholated cigarettes, as opposed to differences in menthol levels (as is the case for the new and predicate products here). Therefore, at this time, based on the available scientific evidence, the change in menthol content between the new and predicate products do not cause the new products to raise different questions of public health. Thus, this deficiency relating to menthol should not be conveyed to the applicant.

5. All of your SE Reports provide conflicting tobacco blend quantities in the "Tobacco Blend" and "Design Feature" of the amended SE Reports. Specifically, the total weight of tobacco reported in the "Tobacco Blend" section differs from the "Tobacco Weight per Cigarette" given in the "Design Feature" tab. For example, you report that the predicate product in SE0003012 contains (b) (4) /cig tobacco, according to the "Design Feature" section, and (b) (4) /cig tobacco, according to the "Tobacco Blend" section. Clarify the total amount of tobacco and the quantities of each tobacco type contained in the blend for the new and predicate products.

6. All of your SE Reports include data comparing the quantities of HPHCs in the new and remanufactured predicate products. However, your SE Reports lack detailed information of methods (b) (4) used by (b) (4), which is necessary to fully evaluate the data. Provide the following information about the HPHC testing so that we can fully evaluate the HPHC data:

    a. Reference product datasets (e.g., 1R6F)
    b. Quantitative test protocols and method used
    c. A summary of the results for all testing performed

    If your test methods are national or international test standards, identify any deviations from those standards.[9]

7. All of your SE Reports list mainstream smoke yields of tar, nicotine, and carbon monoxide (TNCO) and three HPHCs (acetaldehyde, benzene and B[a]P) under ISO and CI smoking regimens. However, there are discrepancies between the data sets in the (b) (4) Report and Exhibit A of the July 10, 2017 amendment. For example, in the (b) (4) report, nicotine level in mainstream smoke under ISO regimen is (b) (4) mg/cig for the new products of SE0003005 and SE0003006, while Exhibit A shows that the value is (b) (4) mg/cig. In the (b) (4) report, nicotine level in mainstream smoke under CI regimen is (b) (4) mg/cig for the new products of SE0003005 and SE0003006, while the quantity in Exhibit A is (b) (4) mg/cig. Explain the data discrepancies in your amendment and identify the correct data sets for FDA to determine whether the differences in HPHC yields may cause the new products to raise different questions of public health.[10]

8. All of your SE Reports contain some quantities of ingredients that require additional explanation. For example, the values of (b) (4) in seam adhesive are reported as (b) (4) mg/cigarette and (b) (4) mg/cigarette for the new and predicate products respectively and the quantities of (b) (4) in tipping adhesive are (b) (4) mg/cigarette for the new products. Provide justification for reporting range quantities and report absolute values for the corresponding ingredients.

[9] This deficiency will be combined with information in deficiency two of the chemistry section for all SE Reports except SE0002998, SE0003000, SE0003001, and SE0003005 as this deficiency is redundant. This will be modified accordingly in the letter-ready deficiencies.

[10] This sentence should read "Explain the data discrepancies in your amendment and identify the correct data sets for FDA to determine whether the differences in HPHC yields do not cause the new products to raise different questions of public health." The letter-ready deficiencies have been modified accordingly.

9. All of your SE Reports compared the HPHC data of the "present day predicates" to that of the new products. You state that the "present day predicates" were constructed with the same materials and components as all the Smokin Joes products marketed on February 15, 2007. A present day predicate product is a product that is manufactured at the present day consistent with the product composition (e.g., tobacco, ingredients other than tobacco, and materials) and design specifications in place at the time the grandfathered predicate product was originally manufactured. However, you did not submit documentation demonstrating that the manufacture of the predicate products at present day reflects the grandfathered predicate product at the time of the original manufacture. Confirm whether there is any difference between the "present day predicates" and corresponding grandfathered predicate products. If inconsistency difference exists in the product composition and design parameters between the "present day predicates" and corresponding predicate products, provide detailed information of the difference for FDA to determine whether the "present day predicates" are reflective of the grandfathered predicate products for all SE Reports. For example, if there is a difference in tobacco grade, provide information on the tobacco grades and grading system. Also, provide a rationale for each difference with evidence and a scientific discussion for why the difference does not cause the new products to raise different questions of public health.[11]

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a chemistry perspective.

4.2. ENGINEERING

An engineering review was completed by Julie Morabito on February 26, 2015. A memo to file was completed by Julie Morabito on September 5, 2017 updating the engineering review in order to review amendments received in response to the General Correspondence Letter after the review was finalized.

[11] This sentence is included in error, and has been removed from the letter-ready deficiencies.

The final engineering review concludes that the new tobacco products have different characteristics related to product engineering compared to the corresponding predicate tobacco products and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiencies that have *not* been adequately resolved:

1. All of your SE Reports provide information on the design parameters for the new and predicate products. However, your SE Reports do not include all of the design parameters needed to fully characterize the new and predicate products. In order to adequately characterize the products, key design parameters need to be compared. Additionally, your SE Reports indicate that FSC cigarette paper is used in the new products. However, the tables you provided list "band width/spacing (mm)" and do not clearly indicate whether the target specification and range limits for "band width/spacing (mm)" correspond to band width or to band space. Accordingly, clarify your use of the term "band width/spacing (mm)".

   Furthermore, you provide "band diffusion (cm/s)" rather than band porosity (CU). Band diffusion is not interchangeable with band porosity.

   Therefore, provide the actual (not approximate) target specification and upper and lower range limits for all of the following cigarette design parameters for each new or predicate product, as indicated:

   a. Tobacco filler mass (mg; predicate products only)
   b. Cigarette paper band porosity (CU; new products only)
   c. Cigarette paper band width (mm; new products only)
   d. Cigarette paper band space (mm; new products only)

   In addition, provide the upper and lower range limits for all of the following cigarette design parameters for each new and predicate product unless otherwise indicated:

   e. Cigarette circumference (mm; predicate products only)
   f. Cigarette draw resistance (mm H_2O)
   g. Tobacco rod density (g/cm^3; predicate products only)
   h. Total denier (g/9,000m)
   i. Denier per filament (DPF)
   j. Filter density (g/cm^3)
   k. Filter length (mm)
   l. Filter ventilation (%)

   For each of the above parameters, provide the necessary data on a per unit of product basis (e.g., filter length should be reported in mm per cigarette). If a design parameter is not applicable (e.g., band porosity if the cigarette paper does not contain bands), state as such and provide a scientific rationale.

   If a difference exists between the new and corresponding predicate products, provide a rationale for each difference in the target specification and range limits with evidence

and a scientific discussion for why the difference does not cause the new product to raise different questions of public health.

Note that filter density, denier per filament, and total denier are necessary because filter efficiency (%) was not provided. As an alternate to submitting the information described above for filter density, denier per filament, and total denier, you may provide target specification and upper and lower range limits for filter efficiency.

2. All of your SE Reports include design parameter specifications but do not include data confirming that specifications are met. Provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for all of the following cigarette design parameters for each new and predicate product unless otherwise indicated:

    a. Cigarette draw resistance (mm H_2O)
    b. Tobacco filler mass (mg)
    c. Tobacco oven volatiles (OV) (%)
    d. Filter ventilation (%)
    e. Cigarette paper base paper basis weight (g/m^2)
    f. Cigarette paper base paper porosity (CU)
    g. Cigarette paper band porosity (CU; new products only)
    h. Total denier (g/9,000m)
    i. Denier per filament (DPF)
    j. Filter density (g/cm^3)
    k. Filter pressure drop (mm H_2O)

    For each of the above parameters, provide the needed data on a per unit of product basis (e.g., filter pressure drop should be reported in mm per cigarette). If a design parameter is not applicable (e.g., band porosity if the cigarette paper does not contain bands), state as such and provide a scientific rationale.

    Certificates of analysis from the material supplier may satisfy this deficiency. If you choose to address this deficiency by providing certificates of analysis for any of the parameters listed above, the certificates of analysis must include a target specification; quantitative acceptance criteria; parameter units; test data average value; and either the standard deviation of the test data or the minimum and maximum values of the test data.

    Additionally, for the design parameters listed above that were tested according to national or international standards, identify the standards and state what deviations, if any, from the standards occurred.

    Note that test data for filter density, denier per filament, and total denier are necessary because filter efficiency (%) was not provided. If you choose to provide filter efficiency in place of filter density, denier per filament, and total denier, provide test data as described above for filter efficiency.

3. All of your SE Reports indicate that you may employ the use of multiple materials for cigarette paper for material supply security. However, it is unclear whether you use multiple materials for cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesives for the new and predicate products, based on the material ingredients information provided in your original SE Reports. Clarify the materials for which multiple interchangeable materials are used in all of the new and predicate products. In accordance with section 910(a)(1)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), each product modification, including use of an alternate material, constitutes a new tobacco product. A material is an alternate material if it has any difference in composition (e.g., ingredients, additives, and biological organisms), or design parameters (target specifications or range limits).[12] Each identified new and predicate product must consist of a single combination of cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesive materials. Based on the components which you confirm employ the use of multiple interchangeable materials, identify the following:

    a. Every unique material combination in the predicate product that you are comparing to the new product in accordance with Section 910(a)(2)(B) of the FD&C Act.[13]
    b. Every unique material combination in the new tobacco product under Section 905(j)(2) of the FD&C Act. Each specific combination of materials will be considered a single new tobacco product and evaluated individually in accordance with Section 910(a)(2)(B) of the FD&C Act.[14]

    Provide the list of ingredients and ingredient quantities for each identified material in each new and predicate product.

    Provide the target specifications and upper and lower range limits for all of the following design parameters for each material in each new and predicate product:

    c. Cigarette base paper basis weight
    d. Cigarette base paper porosity
    e. Cigarette base paper band width
    f. Cigarette base paper band space
    g. Filter total denier
    h. Filter denier per filament
    i. Filter density
    j. Filter pressure drop
    k. Filter length

[12] This sentence warrants correction and clarification. A new tobacco product includes any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007. Section 910(a)(1)(B) of the FD&C Act. A difference in design parameter that does not modify the tobacco product, *e.g.*, a tightening of a design parameter range, does not result in a new tobacco product. This deficiency has been edited to reflect the foregoing in the letter-ready comments.

[13] The statutory references in this sentence are incorrect and were included by the third cycle engineering reviewer in error. The letter-ready deficiencies have been edited to remove the statutory reference.

[14] Same as note above.

l. Filter ventilation
m. Tipping paper length
n. Cigarette draw resistance

Provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for all of the following design parameters for each material in each new and predicate product:

o. Cigarette base paper basis weight
p. Cigarette base paper porosity
q. Cigarette band porosity
r. Filter total denier
s. Filter denier per filament
t. Filter density
u. Filter pressure drop
v. Filter ventilation
w. Cigarette draw resistance

Certificates of analysis (COAs) from the material supplier may satisfy this portion of the deficiency. If you choose to address this deficiency by providing COAs for any of the parameters listed above, the COAs must include target specification; quantitative acceptance criteria; parameter units; test data average value; and either the standard deviation of the test data or the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

Additionally, if a difference exists between the new and predicate product identified for each SE Report, provide justification for the difference and a scientific rationale for why the difference does not cause the new product to raise different questions of public health. Some options for demonstrating that the differences do not cause the new products to raise different questions of public health include the following:

Option 1: Identify a single unique predicate product (with corresponding ingredients), composed of a single cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesive material. Additionally, select and identify a single new product (with corresponding ingredients), composed of a single cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesive material. The identified new product will be the only version of the new product considered for evaluation of substantial equivalence with the identified predicate product. The identified new product will also be the only material combination permitted. Therefore, alternate materials will not be permitted. Provide target specifications, upper and lower range limits, and test data generated from testing of cigarette base paper basis weight, cigarette base paper porosity, cigarette paper band porosity, filter total denier, filter denier per filament, filter density, filter pressure drop, filter ventilation, and cigarette draw resistance and HPHCs for the unique new and predicate products, based on the single combination of cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesive materials identified. If a difference exists between the single identified new product and the single identified predicate product, provide scientific evidence and a rationale

for why the difference does not cause the new product to raise different questions of public health.

Option 2: If you need to list alternate materials for the new and predicate products, you may choose to demonstrate that the use of alternate cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesive materials does not cause the new products to raise different questions of public health. To do this, identify every unique new and predicate product that may result from the integration of each combination of alternate materials. Each identified new and predicate product must consist of a cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesive material combination. Provide target specifications, upper and lower range limits, and test data generated from testing of cigarette base paper basis weight, cigarette base paper porosity, cigarette paper band porosity, filter total denier, filter denier per filament, filter density, filter pressure drop, filter ventilation, and cigarette draw resistance and HPHCs for each identified new and predicate product, based on all possible combinations of cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesive materials. If a difference exists between the new and predicate products identified for each SE Report, provide scientific evidence and a rationale for why the difference does not cause the new product to raise different questions of public health.

Option 3: If you need to list alternate materials for the new and predicate products, you may choose to provide a "bracketing" approach to demonstrate that the alternate materials in the new and predicate products do not cause the new products to raise different questions of public health. To do this, specify two unique versions[15] of the new product, and if the predicate product contains alternate materials, two unique versions of the predicate product:

- For one of the unique versions of the new product, identify a single set of alternate materials that result in the highest HPHC yields generated through integration of the alternate materials.
- For the other unique version of the new product, identify a single set of alternate materials that result in the lowest HPHC yields generated through integration of the alternate materials.
- For one of the unique versions of the predicate product, identify a single set of alternate materials that result in the highest HPHC yields generated through integration of the alternate materials.
- For the other unique version of the predicate product, identify a single set of alternate materials that result in the lowest HPHC yields generated through integration of the alternate materials.

Provide a justification for why each version of the new and predicate product is representative of the highest and lowest HPHC yield in the products. Additionally, for each version specified, provide target specifications, upper and lower range limits, and test data generated from testing of cigarette base paper basis weight, cigarette base

[15] To clarify, the phrasing "two unique versions of the new tobacco product" is not intended to suggest that the use of alternate materials would not result in multiple tobacco products. Rather, the phrasing is used only for convenience/instruction.

paper porosity, cigarette paper band porosity, filter total denier, filter denier per filament, filter density, filter pressure drop, filter ventilation, and cigarette draw resistance and HPHCs for all of the identified new and predicate products. If a difference exists between the identified new and predicate products, provide scientific evidence and a rationale for why the difference does not cause the new product to raise different questions of public health.

All predicate product materials selected or used for comparison or bracketing must have been used in the predicate tobacco product as of February 15, 2007 and have been commercially marketed (other than for test marketing).
You stated that you no longer manufacture the predicate product and, therefore, are unable to provide the necessary design parameter data. Even if you no longer manufacture the predicate product, you still need to fully characterize the new and predicate products and, if the characteristics are different, demonstrate that the new products do not raise different questions of public health. Some potential options for obtaining data on the predicate products include, but are not limited to:

- Manufacture the predicate products at present day, consistent with the product composition and design specifications in place at the time the grandfathered predicate product was originally manufactured. In this case, design parameter data should be accompanied by documentation demonstrating that the manufacture of the predicate product at present day is reflective of the grandfathered predicate product at the time of original manufacture.
- Submit design parameter data for products other than the predicate products (referred to as surrogate tobacco products) that can be extrapolated to the predicate products. In this case, data for the surrogate tobacco products could be submitted in place of data for the predicate products. However, information and data need to be provided to demonstrate that data for the surrogate tobacco products can be extrapolated to the predicate products. For example, the design parameter specifications for the predicate and surrogate products should be compared and an explanation provided for how each difference in specification would affect the extrapolation from the surrogate to predicate products.

4. All of your SE Reports provide target specifications for 'cigarette pressure drop open', a term that is interchangeable with the term 'overall cigarette draw resistance'. However, there is an inconsistency in the difference to overall cigarette draw resistance for (b) (4) that is not present in your other SE Reports.[16] In SE0002998, SE0003000-SE0003001, SE0003014, and SE0003022-SE0003023, the denier per filament, filter density, filter length, cigarette circumference, and tobacco rod density decreased in the new products. However, the overall cigarette draw resistance increased in all of the new products in these eight SE Reports. Because the combined differences to denier per filament, filter density, filter length, cigarette circumference, and tobacco rod density would be expected to result in similar and proportional differences to overall cigarette draw resistance, it is unclear why the overall cigarette draw resistance

[16] (b) (4) was withdrawn and this sentence will not be included in the letter-ready comments to the applicant.

increases in SE0002998, SE0003000-SE0003001, SE0003014, and SE0003022-SE0003023. Therefore, in order to fully characterize the new and predicate products for evaluation of Substantial Equivalence, confirm that the values provided for overall cigarette draw resistance are accurate. If the values are not accurate, provide new values for overall cigarette draw resistance for the new and predicate products in all of your SE Reports. If any difference exists between the new and corresponding predicate products, provide justification and scientific rationale to demonstrate that the difference does not cause the new products to raise different questions of public health.

5. SE0003005-SE0003006, SE0003012, SE0003015, and SE0003020-SE0003021 indicate that the tipping paper length for the new and predicate products is 27mm, while the filter plug length is 30mm. It is unclear why the provided tipping paper length is less than the provided filter plug length because tipping paper typically extends beyond the filter plug to secure the filter plug to the tobacco rod. To fully characterize the design parameters of the new and predicate products, clarify the length of the tipping paper in these seven SE Reports. If a difference exists between the new and corresponding predicate products, provide a scientific discussion and rationale to justify why the difference does not cause the new products to raise different questions of public health.

6. SE0002998, SE0003000-SE0003001, SE0003014, and SE0003022-SE0003023 indicate that the tobacco rod packing density decreased by 11.1% in the new products. Decreased tobacco rod packing density may decrease the filtration through the tobacco rod, thereby increasing the smoke constituent yields of the cigarette and causing the new products to raise different questions of public health. Therefore, provide justification and scientific rationale for the decrease in tobacco rod packing density to demonstrate that the differences do not cause the new products to raise different questions of public health.

7. All of your SE Reports indicate that the base paper porosity decreased by 8.3% in the new products. Decreased base paper porosity may result in increased smoke constituent yields through decreased air dilution of the smoke. Therefore, provide scientific rationale and justification for the decreased base paper porosity to demonstrate why this difference does not cause the new products to raise different questions of public health.

8. SE0002998, SE0003000-SE0003001, SE0003014, and SE0003022-SE0003023 indicate that there are differences in the filter design parameters of the new product. In these eight SE Reports, the denier per filament, filter density, and filter length decreased. However, the pressure drop decreased in the new product of SE0002998 while the pressure drop increased in the new products in SE0003000-SE0003001, SE0003014, and SE0003022-SE0003023. Because the differences to denier per filament, filter density, and filter length would be expected to result in similar and proportional differences to filter pressure drop, it is unclear why the pressure drop increases in one of these SE reports but decreases in five of these SE Reports. Therefore, in order to fully characterize the new and predicate products, provide a scientific explanation to clarify the unexpected differences to filter pressure drop among the other collective differences to filter design parameters in the new products in these SE Reports.

9. SE0002998, SE0003000-SE0003001, SE0003005-SE0003006, SE0003012, SE0003014, and SE0003020-SE0003023 indicate that there are several differences in filter design parameter specifications. Some of these differences have the potential to cause the new products to raise different questions of public health, while others do not. The combination of the differences in the filter design parameters (e.g., filter denier per filament, filter density, filter pressure drop, filter length) in each of these SE Reports may impact smoke constituent yields of the new product. Therefore, provide a scientific discussion and rationale, including published or unpublished data, to demonstrate that the combination of differences to the filter design parameters do not cause the new products to raise different questions of public health for each of the following groups:

    a. In SE0002998, there was a (b) (4) decrease in filter denier per filament, a less than 5% decrease in filter density, a 11.1% decrease in filter pressure drop and a 20% decrease in filter length between the new and predicate products.
    b. In SE0003000, SE0003001, SE0003014, SE0003022, and SE0003023, there was a (b) (4) decrease in filter denier per filament, a 37.9% increase in filter pressure drop, a 20% decrease in filter length, and, in SE0003014, a 8.3% decrease in density between the new and predicate products.
    c. In SE0003005, SE0003006, SE0003012, SE0003020, and SE0003021, there was a 11.1% increase in filter pressure drop and a 5.0-5.2% decrease in filter density between the new and predicate products.

    While not the only way to address this deficiency, one potential way would be to provide target specifications, upper and lower range limits, and complete test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for filter efficiency (%) of the new and corresponding predicate products.

10. All of your SE Reports provide average values for puff count for all of the new and predicate products, but you do not provide test protocols or data sets for the new and predicate products for puff count for all SE Reports. Complete test data is necessary to fully characterize the new and predicate products for evaluation of substantial equivalence. Accordingly, provide the test protocol and data sets for puff count for all of the new and predicate products for SE0002998, SE0003000, SE0003001, SE0003005, SE0003006, SE0003012, SE0003014, SE0003015, SE0003020, SE0003021, SE0003022, and SE0003023. Additionally, for SE0002998, SE0003000, SE0003001, SE0003022, and SE0003023, the puff count of the new products is between 12.8% and 39.8% higher than the puff count of the predicate products. An increase in puff count may increase smoke constituent yields, thereby causing the new products to raise different questions of public health. Therefore, provide scientific justification for why the difference in puff count for SE0002998, SE0003000, SE0003001, SE0003022, and SE0003023 does not cause the new products to raise different questions of public health.

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from an engineering perspective.

4.3. TOXICOLOGY

A toxicology review was completed by Kelly Brant on July 15, 2016. A memo to file was completed by Pei-Hsuan Hung on August 29, 2017, updating the toxicology review in order to review amendments received after the review was finalized.

The final toxicology review concludes that the new tobacco products have different characteristics related to product toxicity compared to the corresponding predicate tobacco products and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiency that has *not* been adequately resolved:

1. All of your SE Reports provide select HPHC testing data for all the new and remanufactured ('present day') predicate products in the amendment received on July 10, 2017. There are ingredients added or increased in the combustible parts of the new products (tobacco, cigarette paper and seam adhesive). For example, SE0002998, SE0003000, SE0003001, SE0003005 and SE0003006 indicate the new tobacco products contain added (b) (4) [redacted] which reportedly contains (b) (4) [redacted] ingredients not found in the corresponding predicate products. The HPHC values you provided indicate increases in the new products when compared with the corresponding predicate products for the SE Reports below:

   <u>Acetaldehyde</u>
   ISO: SE0003000 (22.02%), SE0003001 (22.02%)
   HCI: SE0003000 (23.05%), SE0003001 (23.05%), SE0003012 (16.92%), SE0003014 (16.81%)

   <u>Benzene</u>
   HCI: SE0002998 (10.74%), SE0003000 (15.79%), SE0003001 (15.79%), SE0003012 (25%)

   <u>Benzo(a)pyrene</u>
   ISO: SE0002998 (53.17%), SE0003014 (54.29%)
   HCI: SE0002998 (26.64%), SE0003014 (24.21%), SE0003015 (8.55%)

   <u>Carbon monoxide</u>
   ISO: SE0002998 (27.11%), SE0003000 (20.8%), SE0003001 (20.8%), SE0003005 (4.79%), SE003006 (4.79%), SE0003014 (5.69%)
   HCI: SE0003000 (24.68%), SE0003001 (24.68%), SE0003012 (25.19%), SE0003015 (23.44%)

   The increase of HPHC yields can result from the pyrolysis of ingredients added or increased in the new products. Inhalation exposures to the pyrolysis products of many of these ingredients in top and casing flavors, cigarette paper and seam adhesives have been associated with toxicological effects relevant to human health, including adverse effects on the respiratory system. You cited one published literature (Coggins, et al., 2013) to support that the ingredient changes in adhesives do not cause the new products to raise different questions of public health. However, you did not provide a

rationale explaining how the information generated using the experimental cigarettes in the cited study can be extrapolated to the specific new and predicate products listed in your SE Reports. Provided scientific evidence that the addition or increase of ingredients in the specific new products relative to their corresponding predicate products and their combustion products do not cause the new products listed in your SE Reports to raise different questions of public health was needed. If referencing research studies, you needed to explain how each reference supports the specific comparison between the new and predicate products. You needed to explain how data extrapolated from these references supports the conclusion that the different characteristics in your new products as compared to the corresponding predicate products do not cause the new products to raise different questions of public health.[17]

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a toxicology perspective.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(b), issuance of an order finding a tobacco product Not Substantially Equivalent (NSE) under section 910(a) of the FD&C Act is categorically excluded and, therefore, normally does not require the preparation of an environmental assessment (EA) or environmental impact statement. FDA has considered whether there are extraordinary circumstances that would require the preparation of an EA and has determined that none exist.

6. CONCLUSION AND RECOMMENDATION

The following are the key differences in characteristics between the new and corresponding predicate tobacco products:

- Numerous changes in non-tobacco ingredients
- Changes in tobacco blend in (b) (4) [redacted]
- Changes in product design features

The applicant has failed to demonstrate that these differences in characteristics do not cause the new tobacco products to raise different questions of public health. The applicant did not provide information to uniquely identify all of the non-tobacco ingredients and tobacco blend, and similarly did not provide sufficient information on the product design features in the new and corresponding predicate tobacco products. Without this information, the composition and design of the new and corresponding predicate products cannot be fully characterized for SE determination. As a result, FDA cannot perform a complete evaluation to determine whether there are differences between

[17] I agree with Chemistry deficiencies 2 and 9, which explain why the HPHC data submitted by the applicant is inadequate and cannot be used to identify differences in HPHC yields between the new and predicate tobacco products. While the submitted data cannot be relied on to determine if there are actual differences in HPHC yields, the submitted data shows increases in HPHC yields (referred to here as "apparent increases"). The applicant did not explain why these apparent increases in HPHC yields do not cause the new products to raise different questions of public health. This toxicology deficiency should be edited to discuss the apparent increases in HPHCs. The edits will be made in the letter ready deficiencies that are to be conveyed to the applicant.

the new and corresponding predicate product that may cause the new products to raise different questions of public health. Although the applicant provides some HPHC yields in mainstream smoke under ISO and CI smoking regimens, there is insufficient information to determine whether the methods used by the testing laboratory to obtain these yields is considered acceptable. More specifically, complete datasets, number of replicates, standard deviations, quantitative test protocols, and storage conditions are not provided to make a scientific comparison between the measured HPHC yields between the new and predicate tobacco products. Thus, the applicant did not provide adequate method information to fully evaluate the validity of the HPHC data provided. Furthermore, the applicant provided remanufactured predicate products, however, the applicant has failed to provide information on the remanufactured predicate products to demonstrate that they reflect the grandfathered predicate products at the time of original manufacture. Additionally, the new products in SE0003006, SE00030012, SE0003014, SE0003015, SE0003020 – SE0003023 have increased amounts of (b) (4) and (b) (4) as compared to the predicate products, and the applicant did not provide sufficient information to demonstrate that these differences do not cause the new products to raise different questions of public health. There is also a change in container closure system from soft pack to hard pack for SE0003001 and SE0003020; however, this change does not affect the characteristics of the consumable portion of the tobacco product and, therefore, does not cause the new product to raise different questions of public health. Furthermore, the applicant has failed to respond to any of the deficiency letters issued by FDA which sought information necessary to make an SE determination. Therefore, the applicant has failed to provide sufficient information to support a finding of substantial equivalence.

The predicate tobacco products meet statutory requirements because they are grandfathered products (i.e., were commercially marketed in the United States other than exclusively in test markets as of February 15, 2007).

The chemistry, engineering, and toxicology reviews conclude that the new tobacco products have different characteristics compared to the corresponding predicate tobacco products and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. I concur with these reviews and recommend that NSE order letters be issued.

Because the proposed action is issuing NSE orders, it is a class of action that is categorically excluded under 21 CFR 25.35(b). FDA has considered whether there are extraordinary circumstances that would require the preparation of an environmental assessment and has determine that none exist. Therefore, the proposed action does not require preparation of an environmental assessment or an environmental impact statement.

NSE order letters should be issued for the new tobacco products in SE0002998, SE0003000, SE0003001, SE0003005, SE0003006, SE0003012, SE0003014, SE0003015, and SE0003020 - SE0003023, as identified on the cover page of this review.

1. All of your SE Reports provide information about the tobacco and ingredients added to the tobacco in the new and predicate products, but limited information on the grades were provided. The information provided for the tobacco did not include sufficient detail to fully identify the composition of the new and predicate products. For example, we are unable to understand the meaning of the tobacco grades: (b) (4) . Furthermore, (b) (4)

(b) (4) for the new product. It is not clear why one grade is listed twice within the same type of tobacco. We needed additional information that uniquely identifies the tobacco and other ingredients used in the new and predicate products to assess whether there are any differences between the new and predicate product and, if so, to determine whether those differences do not cause the new product to raise different questions of public health. You did not provide a detailed list uniquely identifying information for all non-tobacco ingredients (e.g., CAS #, grade/purity, function) and for all tobacco (e.g., tobacco grading system) needed to fully characterize the new and predicate products. If composition differences exist between the new and predicate products, you would also need to provide a rationale for each difference with evidence and a scientific discussion for why the differences do not cause the new product to raise different questions of public health.

2. SE0003006, SE0003012, SE0003014, SE0003015, and SE0003020 – SE0003023 provide data comparing the quantities of HPHCs in the new and remanufactured predicate products, also known as a surrogate predicate product, by submitting the amendments dated March 10, 2017 and July 10, 2017. However, your SE Report lacks HPHC yields to fully evaluate changes in (b) (4) and (b) (4) in the new product compared to the surrogate predicate product. These ingredient differences between the new and surrogate predicate product may cause the new product to raise different questions of public health. You needed to provide scientific evidence and rationale to address why these differences do not cause the new products to raise different questions of public health. One way you may have provided such evidence is by providing measured mainstream smoke yields for formaldehyde and acrolein.

   These HPHC measurements would have helped to determine whether these ingredients cause the new product to raise different questions of public health. For example, mainstream smoke yields of formaldehyde and acrolein are needed because (b) (4) may be thermally decomposed to formaldehyde and acrolein, while (b) (4) can be pyrolyzed to acrolein. Higher levels of (b) (4) and (b) (4) in tobacco products may result in higher quantities of formaldehyde and acrolein in mainstream smoke. The measurement of the HPHC quantities under both ISO and CI smoking regimens would best characterize the delivery of the constituents from these products. FDA suggests that appropriate measures be taken to minimize data variability and systematic bias. The suggested measures include, but are not limited to, using the same laboratory, the same type of smoking machine, the same methods, similar sample storage conditions and duration, and testing within similar timeframe. If you decided to measure select HPHCs, you needed to provide the following information about all HPHC testing so that FDA was able to fully evaluate the differences in HPHC quantities between the new and remanufactured predicate products:

   a. Reference product datasets (e.g., 1R6F)
   b. Quantitative test protocols and method used
   c. Testing laboratory and their accreditation(s)
   d. Length of time between date(s) of manufacture and date(s) of testing
   e. Number of replicates
   f. Standard deviation(s)
   g. Complete data sets
   h. A summary of the results for all testing performed

i. Storage conditions prior to initiating testing If your test methods are national or international test standards, identify any deviations from those standards

3. All of your SE Reports list ingredient quantities as percentages but do not specify the original units of the numerator and denominator, or define the denominator (e.g., per cigarette, per gram). For some ingredients listed, your SE Report does not provide any quantities. In order for FDA to fully understand the composition of the new and predicate products and make a determination of substantial equivalence, you needed to provide ingredient quantities as mass per unit of use (e.g., mg/cigarette).

4. All of our SE Reports provide conflicting tobacco blend quantities in the "Tobacco Blend" and "Design Feature" in the original SE Report compared to the amendment to your SE Report. Specifically, the total weight of tobacco reported in the "Tobacco Blend" section differs from the "Tobacco Weight per Cigarette" given in the "Design Feature" tab. In order to understand the tobacco blend, clarification regarding the total amount of tobacco and the quantities of each tobacco type contained in the blend for the new and predicate products is needed.

5. All of your SE Reports include data comparing the quantities of HPHCs in the new and remanufactured predicate products. However, your SE Report lacks detailed information of methods (b) (4) , which is necessary to fully evaluate the data. You needed to provide the following information about the HPHC testing so that we can fully evaluate the HPHC data:

    a. Reference product datasets (e.g., 1R6F)
    b. Quantitative test protocols and method used
    c. A summary of the results for all testing performed

6. All of your SE Reports list mainstream smoke yields of TNCO and three HPHCs (acetaldehyde, benzene and B[a]P) under ISO and CI smoking regimens. However, there are discrepancies between the data sets in the (b) (4) Report and Exhibit A of your July 10, 2017 amendment. For example, in the (b) (4) report, the nicotine level in mainstream smoke under the ISO and CI regimen is different than what is reported in Exhibit A. You needed to explain the data discrepancies in your amendment and identify the correct data sets for FDA to determine whether the differences in HPHC yields do not cause the new product to raise different questions of public health.

7. All of your SE Reports contain some quantities of ingredients that require additional explanation. For example, the values of (b) (4) in seam adhesive are reported as (b) (4) mg/cigarette and (b) (4) mg/cigarette for the new and predicate products, respectively, and the quantities of (b) (4) in tipping adhesive are (b) (4) mg/cigarette for the new product. You needed to provide justification for reporting range quantities for these ingredients.

8. All of your SE Reports compared the HPHC data of the "present day predicate" to that of the new product. You state that the "present day predicate" was constructed with the same materials and components as all of the Smokin Joes product marketed on February 15, 2007. However, you did not submit documentation demonstrating that the remanufactured

predicate product at present day reflects the grandfathered predicate product at the time of the original manufacture including a side by side comparison of the ingredients, tobacco blends, and product design parameters. You needed to confirm whether there are any differences between the "present day predicate" and grandfathered predicate product. If differences exist in the product composition and design parameters between the "present day predicate" and grandfathered predicate products, you would need to provide detailed information of the differences for FDA to determine whether the "present day predicate" are reflective of the grandfathered predicate product.

9. All of your SE Reports provide information on the design parameters for the new and predicate products. However, your SE Report does not include all of the design parameters needed to fully characterize the new and predicate products. In order to adequately characterize the products, key design parameters need to be compared. Additionally, your SE Report indicates that FSC cigarette paper is used in the new product. However, the tables you provided list "band width/spacing (mm)" and do not clearly indicate whether the target specification and range limits for "band width/spacing (mm)" correspond to band width or to band space. Accordingly, clarification regarding your use of the term "band width/spacing (mm)" is needed. Furthermore, you provided "band diffusion (cm/s)" rather than band porosity (CU). Band diffusion is not interchangeable with band porosity.

   Therefore, you needed to provide the actual (not approximate) target specification and upper and lower range limits for *all* of the following cigarette design parameters for the new or predicate products, as indicated:

   a. Tobacco filler mass (mg) [predicate product only]
   b. Cigarette paper band porosity (CU) [new product only]
   c. Cigarette paper band width (mm) [new product only]
   d. Cigarette paper band space (mm) [new product only]

   In addition, you needed to provide the upper and lower range limits for *all* of the following cigarette design parameters for the new and predicate products, as indicated:

   e. Cigarette circumference (mm) [predicate product only]
   f. Cigarette draw resistance (mm H_2O)
   g. Tobacco rod density (g/cm^3) [predicate product only]
   h. Total denier (g/9,000m)
   i. Denier per filament (DPF)
   j. Filter density (g/cm^3)
   k. Filter length (mm)
   l. Filter ventilation (%)

   For each of the above parameters, you needed to provide the necessary data on a per unit of product basis (e.g., filter length should be reported in mm per cigarette). If a design parameter is not applicable (e.g., band porosity if the cigarette paper does not contain bands), you needed to state as such and provide a scientific rationale.

   If a difference exists between the new and predicate products, you would need to provide a rationale for each difference in the target specification and range limits with evidence and a

scientific discussion for why the difference does not cause the new product to raise different questions of public health.

10. All of your SE Reports include design parameter specifications but do not include data confirming that specifications are met. You needed to provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for *all* of the following cigarette design parameters for the new and predicate product unless otherwise indicated:

    a. Cigarette draw resistance (mm H_2O)
    b. Tobacco filler mass (mg)
    c. Tobacco oven volatiles (OV) (%)
    d. Filter ventilation (%)
    e. Cigarette paper base paper basis weight (g/m2)
    f. Cigarette paper base paper porosity (CU)
    g. Cigarette paper band porosity (CU) [new product only]
    h. Total denier (g/9,000m)
    i. Denier per filament (DPF)
    j. Filter density (g/cm^3)
    k. Filter pressure drop (mm H_2O)

    For each of the above parameters, you needed to provide the data on a per unit of product basis (e.g., filter pressure drop should be reported in mm per cigarette). If a design parameter is not applicable (e.g., band porosity if the cigarette paper does not contain bands), you needed to state as such and provide a scientific rationale.

    Certificates of analysis from the material supplier may have satisfied this issue. If you chose to address this issue by providing certificates of analysis for any of the parameters listed above, the certificates of analysis needed to include a target specification; quantitative acceptance criteria; parameter units; test data average value; and either the standard deviation of the test data or the minimum and maximum values of the test data. Additionally, for the design parameters listed above that were tested according to national or international standards, you needed to identify the standards and state what deviations, if any, from the standards occurred.

11. All of your SE Reports indicate that you may employ the use of multiple materials for cigarette paper for material supply security. However, it is unclear whether you use multiple materials for cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesives for the new and predicate products, based on the material ingredients information provided in your SE Report. You needed to clarify the materials for which multiple interchangeable materials are used in the new and predicate products. In accordance with section 910(a)(1)(B) of the FD&C Act, each product modification, including use of an alternate material, constitutes a new tobacco product. A material is an alternate material if, for example, it has any difference in composition (e.g., ingredients, additives, and biological organisms). Each identified new and predicate product must consist of a single combination of cigarette base paper, filter tow, plug wrap, tipping paper, inks, and seam adhesive materials. Based on the components which you confirm employ the use of multiple interchangeable materials, you needed to identify the following:

a. Every unique material combination in the predicate product that you are comparing to the new product.
b. Every unique material combination in the new tobacco product. Each specific combination of materials will be considered a single new tobacco product and evaluated individually.

You needed to provide the list of ingredients and ingredient quantities for each identified material in each new and predicate product. Additionally, you needed to provide the target specifications and upper and lower range limits for *all* of the following design parameters for each material in the new and predicate products:

c. Cigarette base paper basis weight
d. Cigarette base paper porosity
e. Cigarette base paper band width
f. Cigarette base paper band space
g. Filter total denier
h. Filter denier per filament
i. Filter density
j. Filter pressure drop
k. Filter length
l. Filter ventilation
m. Tipping paper length
n. Cigarette draw resistance

You also needed to provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for *all* of the following design parameters for each material in the new and predicate products:

o. Cigarette base paper basis weight
p. Cigarette base paper porosity
q. Cigarette band porosity
r. Filter total denier
s. Filter denier per filament
t. Filter density
u. Filter pressure drop
v. Filter ventilation
w. Cigarette draw resistance

Certificates of analysis from the material supplier may have satisfied this issue. If you chose to address this issue by providing certificate of analysis for any of the parameters listed above, the certificate of analysis needed to include target specification; quantitative acceptance criteria; parameter units; test data average value; and either the standard deviation of the test data or the minimum and maximum values of the test data.

Refer to the Preliminary Finding letter issued by FDA on February 13, 2018, which provided instructions/options on some approaches that could be used to address this issue.

12. SE0002998, SE0003000, SE0003001, SE0003014, SE0003022, and SE0003023 indicate that the denier per filament, filter density, filter length, cigarette circumference, and tobacco rod density decreased in the new product and the overall cigarette draw resistance increased in the new product. Because the combined differences to denier per filament, filter density, filter length, cigarette circumference, and tobacco rod density would be expected to result in similar and proportional differences to overall cigarette draw resistance, it is unclear why the overall cigarette draw resistance increased. Therefore, in order to fully characterize the new and predicate products, you needed to confirm that the values provided for overall cigarette draw resistance are accurate. If the values are not accurate, you needed to provide new values for overall cigarette draw resistance for the new and predicate products. If any difference exists between the new and predicate products, you needed to provide a justification and scientific rationale to demonstrate that the difference does not cause the new product to raise different questions of public health.

13. SE0003005, SE0003006, SE0003012, SE0003015, SE0003020, and SE0003021 indicate that the tipping paper length for the new and predicate product is 27mm, while the filter plug length is 30mm. It is unclear why the provided tipping paper length is less than the provided filter plug length because tipping paper typically extends beyond the filter plug to secure the filter plug to the tobacco rod. To fully characterize the design parameters of the new and predicate product, you needed to clarify the length of the tipping paper. If a difference exists between the new and predicate product, you needed to provide a scientific discussion and rationale to justify why the difference does not cause the new product to raise different questions of public health.

14. SE0002998, SE0003000, SE0003001, SE0003014, SE0003022, and SE0003022 indicate that the tobacco rod packing density decreased by 11% in the new product. Decreased tobacco rod packing density may decrease the filtration through the tobacco rod, thereby increasing the smoke constituent yields of the cigarette and causing the new product to raise different questions of public health. While you provided select HPHCs, complete information on the analytical methods was not provided in order to determine the validity of the data, therefore limiting a complete analysis on the influence on tobacco rod packing density on HPHC yields. Therefore, you needed to provide scientific evidence and rationale for why the decrease in tobacco rod packing density does not cause the new product to raise different questions of public health.

15. All of your SE Reports indicate that the base paper porosity decreased by 8% in the new product. Decreased base paper porosity may result in increased smoke constituent yields through decreased air dilution of the smoke. While you provided select HPHCs, complete information on the analytical methods was not provided in order to determine the validity of the data, therefore limiting a complete analysis on the influence on base paper porosity on HPHC yields. Therefore, you needed to provide scientific evidence and rationale for why the decreased base paper porosity does not cause the new product to raise different questions of public health.

16. SE0002998, SE0003000, SE0003001, SE0003014, SE0003022, and SE0003023 indicate that there are differences in the filter design parameters of the new and predicate products. The denier per filament, filter density, filter length, decreased in the new product while the

pressure drop decreased in the new product of SE0002998 and increased in the new products in SE0003000, SE0003001, SE0003014, SE0003022, and SE0003023. Because the differences to denier per filament, filter density, and filter length would be expected to result in similar and proportional differences to filter pressure drop, it is unclear why the pressure drop increases in one of these SE Reports but decreases in the other five SE Reports. Therefore, in order to fully characterize the new and predicate products, you needed to provide a scientific explanation to clarify the unexpected differences to filter pressure drop among the other collective differences to filter design parameters in the new product.

17. SE0002998, SE0003000, SE0003001, SE0003005, SE0003006, SE0003012, SE0003014, and SE0003020 – SE0003023 indicate that there are differences in numerous filter design parameter specifications including the following:

    a. SE0002998: a (b) (4) decrease in filter denier per filament, a less than 5% decrease in filter density, a 11% decrease in filter pressure drop and a 20% decrease in filter length
    b. SE0003000, SE0003001, SE0003014, SE0003022, and SE0003023: a (b) (4) decrease in filter denier per filament, a 38% increase in filter pressure drop, and a 20% decrease in filter length,
    c. SE0003014:8.3% decrease in filter density
    d. SE0003005, SE0003006, SE0003012, SE0003020, and SE0003021: a 11% increase in filter pressure drop and a 5.0% decrease in filter density

    Some of these differences have the potential to cause the new product to raise different questions of public health, while others do not. The combination of the differences in the filter design parameters (i.e., filter denier per filament, filter density, filter pressure drop, filter length) may impact smoke constituent yields of the new product. Therefore, you needed to provide scientific evidence and rationale to demonstrate that the combination of differences to the filter design parameters do not cause the new product to raise different questions of public health. One potential way you may have addressed this issue would be to provide target specifications, upper and lower range limits, and complete test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for filter efficiency (%) of the new and predicate product.

18. All of your SE Reports provide average values for puff count for the new and predicate products, but does not provide test protocols or data sets for the new and predicate products for puff count. An increase in puff count may increase smoke constituent yields, thereby causing the new products to raise different questions of public health. While you provided select HPHCs, complete information on the analytical methods was not provided in order to determine the validity of the data, therefore limiting a complete analysis on the influence of puff count on HPHC yields. You needed to provide complete test data in order to fully characterize the new and predicate products. Additionally, you needed to provide the test protocol and data sets for puff count for the new and predicate products and scientific evidence and rationale for why any differences in the puff count does not cause the new product to raise different questions of public health.

19. All of your SE Report indicate ingredients added or increased in the combustible parts of the new products (tobacco, cigarette paper and seam adhesive) that could cause the new products to raise different questions of public health. You submitted HPHC testing data for all the new and remanufactured ('present day') predicate products in the amendment received on July 10, 2017. However, this HPHC data is inadequate because you did not provide sufficient details on the testing methods, protocols, laboratory and its accreditation, etc., and you did not provide enough information (e.g., materials, ingredients, tobacco blend) comparing the remanufactured predicate products used for the HPHC testing to the originally manufactured predicate products. As a result of the former, HPHC data from the remanufactured predicate products cannot be used in place of HPHC data from the originally manufactured products.

    Despite the foregoing, and proceeding on the assumption that the HPHC data is adequate, the HPHC values you provided indicate apparent increases in the new products when compared with the corresponding predicate products for the SE Reports below:

    Acetaldehyde
    ISO: SE0003000 (22.02%), SE0003001 (22.02%)
    HCI: SE0003000 (23.05%), SE0003001 (23.05%), SE0003012 (16.92%), SE0003014 (16.81%)

    Benzene
    HCI: SE0002998 (10.74%), SE0003000 (15.79%), SE0003001 (15.79%), SE0003012 (25%)

    Benzo(a)pyrene
    ISO: SE0002998 (53.17%), SE0003014 (54.29%)
    HCI: SE0002998 (26.64%), SE0003014 (24.21%), SE0003015 (8.55%)

    Carbon monoxide
    ISO: SE0002998 (27.11%), SE0003000 (20.8%), SE0003001 (20.8%), SE0003005 (4.79%), SE003006 (4.79%), SE0003014 (5.69%)
    HCI: SE0003000 (24.68%), SE0003001 (24.68%), SE0003012 (25.19%), SE0003015 (23.44%)

    The apparent increase of HPHC yields can result from the pyrolysis of ingredients added or increased in the new product. Inhalation exposures to the pyrolysis products of many of these ingredients in top and casing flavors, cigarette paper and seam adhesives have been associated with toxicological effects relevant to human health, including adverse effects on the respiratory system. You cited one published literature (Coggins, et al., 2013) to support that the ingredient changes in adhesives do not cause the new product to raise different questions of public health. However, you did not provide a rationale explaining how the information generated using the experimental cigarettes in the cited study can be extrapolated to the specific new and predicate product. You needed to provide scientific evidence that the addition or increase of ingredients in the new product relative to the predicate product and the combustion products do not cause the new product to raise different questions of public health.